oxidation (as defined in Hawley's Condensed Chemical Dictionary © 1993) adding a reducing agent would likely be beneficial in terms of chemical stability. This, however, is not what is truly surprising about the present invention.

As known to one skilled in the art, stabilizing actives using reducing agents usually involves directly combining the reducing agent with the pharmaceutical active. Gallo-Torres ('543) does just this when it combines a stabilizer and the active in a common solvent; ascorbates and prostaglandins are both solubilized, in polyoxyethylene sorbitan esters of fatty acids or polyethylene glycols; see column 2, lines 48-54. On the basis Gallo-Torres's teaching, one skilled in the art would not use a combination of water-soluble reducing agents and water-insoluble actives as is the case in the present invention. Furthermore, the prostaglandin solvents such as polyoxyethylene sorbitan esters of fatty acids would not be effective in solubilizing the reducing agents of the present invention.

Contrary to the examiner's assumption that reducing agents and antioxidants are the same, the reducing agents of the present invention and the stabilizers (antioxidants) disclosed by Gallo-Torres fundamentally are different. Gallo-Torres uses ascorbates to protect the oxygen-susceptible prostaglandin active from atmospheric oxidation. This is considered a true antioxidant. On the other hand, the reducing agent of the present invention does not perform such a function. Reduction reactions involve the reversible loss of electrons without addition of oxygen. It does not per se inhibit atmospheric oxidation. In context of this invention, it is the applicants experience that eliminating the possibility of oxidation of the active using a nitrogen atmosphere during processing (as taught by Gallo-Torres) had little or no effect in stabilizing the claimed compositions.

With regard to '666, Haas teaches at column 3, lines 37-41 that it is essential to the optimum stability of the final product that the composition's pH be maintained in the alkaline range, between 7 and 7.7. Haas' active is ibuprofen. In Haas' pH range, ibuprofen carries a negative charge because it is an acid with a pKa of 4.4. Ibuprofen in the negatively charged state falls outside the scope of the pending claims since the actives claimed herein are "nonionic," thereby facilitating (rather than hindering) mucosal tissue permeability. Furthermore, Haas' pH range limitation indicates that the composition is aqueous (since pH is a measure of the hydrogen ion concentration of aqueous acid-base systems). While the reducing agent of the present invention is solubilized in a small amount of water before being added to the bulk of the composition, the composition of the present invention is not aqueous and doesn't have a pH per se. Even when the composition is diluted in saliva (essentially water), the resulting pH (from about 8 to about 10) falls outside the range taught by Haas.

The composition disclosed by Arias comprises pyrethroids, synthesized compounds of natural pyrethrum and often used as an insecticide, in an aqueous carriers or diluents. As discussed above, the present invention is a stabilized formulation designed for easy entry through the oral mucosal barrier for quick assimilation into the blood stream thereby bypassing the liver. It is critical that such compositions utilize the defined combination of reducing agents, actives and no less importantly the active's anhydrous

solvent. Thus the water content of Arias represents an aqueous composition that does not anticipate or make obvious the present invention.

Wolf et al. discloses ophthalmic preparations for treating glaucoma by applying the compositions disclosed therein directly to the eye. The compositions of the amended claims are oral compositions. On the basis of these amendments, the compositions as disclosed by Wolf are non-analogous and it cannot be the basis for supporting the above novelty rejection.

The applicants, therefore, suggest that the invention as defined by the pending amended claims are novel and unobvious in light of the teachings of the cited references, singularly or combined. As such the pending claims are in form for allowance. It is respectfully requested that the rejection be withdrawn and the amended claims be allowed to issue.

Respectfully submitted,
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VERSION WITH MARKINGS TO SHOW CHANGES MADE

4. (amended) The composition according to claim [3] 21 wherein the reducing agent has an E^0 value from about -.0119V to about +0.250V.

9. (amended) The composition according to claim [8] 21 wherein the pharmaceutical active[s] ha[ve]s a molecular weight of less than 500 grams per mole, is capable of being ionized when in an aqueous solvent and has an octanol-water partition coefficient when in the un-ionized form of at least 100.

10. (amended) The composition according to claim 9 wherein the pharmaceutical active[s] [are] is selected from the group consisting of antitussives, antihistamines, non-sedating antihistamines, decongestants, expectorants, analgesic mucolytics, antipyretic anti-inflammatory agents, local anesthetics and mixtures thereof.

11. (amended) The composition according to claim 10 wherein the concentration of the pharmaceutical active[s] in the solvent is less than or equal to 125% of the percent solubility value of said active.

15. (amended) The composition according to claim 14 wherein the solvent comprises from about 70% to about 99% by weight of the composition.